

**Citation:**

De Walls P, Tairou F, Van Allen MI, Uh SH, Lowry RB, Sibbald B, Evans JA, Van den Hof MC, Zimmer P, Crowley M, Fernandez B, Lee NS, Niyonsenga T. Reduction in neural-tube defects after folic acid fortification in Canada. *N Engl J Med*. 2007 Jul 12; 357 (2): 135-142.

**PubMed ID:** [17625125](#)

**Study Design:**

Trend Study

**Class:**

D - [Click here](#) for explanation of classification scheme.

**Research Design and Implementation Rating:**

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

**Research Purpose:**

- The purpose of this study was to assess changes in the prevalence of neural-tube defects (NTDs) associated with food fortification with folic acid throughout Canada
- Since there was known to be a geographical gradient in the prevalence of neural-tube defects at birth, with higher rates in the eastern provinces than in the western provinces, the authors also tested the hypothesis that the magnitude of the effect of folic acid fortification would vary directly with the baseline rate of the defect.

**Inclusion Criteria:**

Live births, stillbirths and terminations of pregnancies among women residing in seven of the 10 Canadian provinces (Newfoundland and Labrador, Nova Scotia, Prince Edward Island, Quebec, Manitoba, Alberta and British Columbia) from 1993 to 2003.

**Exclusion Criteria:**

- Any live birth, stillbirth or termination before 1993 and after 2002
- Any live birth, stillbirth or termination from the three provinces not listed in the inclusion criteria
- Any birth in the Outaouais region (province of Quebec)
- Subjects with occult spinal dysraphism, including spina bifida occulta, thickened filum terminale, diastematomyelia, caudal regression syndrome, intradural lipoma, lipomeningomyelocele, split notochord and other forms of myelodysplasia. This category of mainly caudal defects may be embryologically distinct from myelomeningocele.

**Description of Study Protocol:****Recruitment**

In each province, the identification of subjects with NTDs relied on multiple sources as follows:

- Newfoundland and Labrador: Newfoundland and Labrador Provincial Medical Genetics Program, provincial live-birth and stillbirth notification forms, maternal fetal medicine referrals to the single tertiary care unit in the province
- Nova Scotia: Provincial Perinatal Database and IWK Health Centre Fetal Anomaly Database
- Prince Edward Island: Provincial Perinatal Database and IWK Health Centre Fetal Anomaly Database
- Quebec: Provincial hospital administrative database MedEcho and infant-death and stillbirth certificates
- Manitoba: Clinical and outcome databases of the Manitoba Maternal Serum Screening Program, the Genetics Prenatal Diagnosis Program and the Genetics and Metabolism Program of the Winnipeg Regional Health Authority
- Alberta: Stillbirth and infant-death certificates and the Provincial Congenital Anomaly Surveillance System supplemented by a survey of all maternity hospitals and children's treatment centers
- British Columbia: Provincial Health Status (Congenital Anomaly) Registry, Vancouver BC Women's and Children's Health Centre databases (including the Provincial Medical Genetics Program), the Spina Bifida Clinic, the Perinatal Diagnosis and Treatment Centre, the Fetal Diagnostic Services Clinic and Victoria Hospital records (including the Fetal Pathology Service, the Medical Genetics Clinic and the Perinatology and Spina Bifida Clinic).

## Design

Trend Study.

## Intervention

Food fortification with folic acid.

## Statistical Analysis

- Prevalence rates for NTDs were calculated as the sum of subjects with the defect in live births, stillbirths and induced abortions, divided by the number of total live births and stillbirths
- Confidence intervals of rates, ratios and differences were calculated by an exact method
- The chi-square test and the Cochran–Armitage test for linear trend in proportions were performed, with the statistical significance level set at 0.05 in two-sided tests
- The relationship between the baseline rate of NTDs in each province and the magnitude of the decrease after fortification began was modeled by testing a series of linear, exponential and power functions. A weight equal to the inverse of the variance of the estimated difference in rate was assigned to each observation.
- Data were analyzed with the use of SAS software, version 8.1 (SAS Institute).

## Data Collection Summary:

- *Dependent variables:* Neural tube defects
- *Timing of measurements:* Data were collected at one time point per subject
- *Independent variables:* Folic acid supplementation of foods.

## Description of Actual Data Sample:

- *Initial N*: 1,909,741 total number of births (2,446 subjects with neural-tube defects)
- *Attrition (final N)*: Same (no dropouts because data were collected at one timepoint)
- *Age*: Fetus or newborn
- *Ethnicity*: Not stated
- *Other relevant demographics*: None given
- *Anthropometrics*: None given
- *Location*: Seven of 10 Canadian Provinces (Newfoundland and Labrador, Nova Scotia, Prince Edward Island, Quebec, Manitoba, Alberta and British Columbia); no territories.

## Summary of Results:

**Table 1. Prevalence of Neural Tube Defects, According to Diagnostic Category, in Seven Canadian Provinces from 1993 through 2002**

Diagnostic Category	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
Anencephaly	1.55	1.59	1.55	1.69	1.50	1.14	0.99	0.86	0.86	0.86
Encephalocele	0.83	0.84	0.89	0.91	0.77	0.62	0.53	0.39	0.41	0.41
Iniencephaly	0.02	0.03	0.01	0.01	0.03	0.01	0.00	0.01	0.00	0.00
Spina bifida	0.19	0.17	0.16	0.18	0.15	0.14	0.12	0.15	0.10	0.10
Unspecified NTD	0.51	0.55	0.47	0.56	0.52	0.36	0.33	0.29	0.34	0.34
All NTD	0.00	0.00	0.01	0.03	0.03	0.01	0.01	0.02	0.01	0.01

**Table 2. Prevalence of Neural Tube Defects, According to Diagnostic Category, in Seven Canadian Provinces from 1993 through 2002**

Diagnostic Category	Pre-Fortification	Partial Fortification	Full Fortification	Rate Ratio	Difference in Rate
Rate (95% confidence interval)					
Anencephaly	0.52 (0.45-0.58)	0.38 (0.28-0.44)	0.32 (0.24-0.38)	0.62 (0.52-0.74)	0.20 (0.13-0.26)
Encephalocele	0.17 (0.09-0.23)	0.12 (0.06-0.19)	0.12 (0.06-0.18)	0.69 (0.51-0.93)	0.05 (0.01-0.09)
Iniencephaly	0.02 (0.01-0.08)	0 (0-0.07)	0.002 (0-0.06)	0.10 (0.01-0.74)	0.02 (0.01-0.03)
Spina bifida	0.86 (0.80-0.92)	0.57 (0.50-0.63)	0.40 (0.35-0.46)	0.47 (0.40-0.55)	0.45 (0.37-0.53)
Unspecified NTD	0.014 (0.01-0.08)	0.01 (0-0.07)	0.012 (0-0.07)	0.85 (0.33-2.22)	0.002(-0.01-0.01)
All NTD	1.58 (1.48-1.64)	1.09 (1.01-1.15)	0.86 (0.80-0.92)	0.54 (0.49-0.60)	0.72 (0.61-0.84)

\* The ratio is the comparison of the full-fortification rate to the pre-fortification rate

\*\* The difference is the pre-fortification rate minus the full-fortification rate

**Table 3. Prevalence of Neural Tube Defects per 1,000 Births, According to Fortification Period.**

Province	Pre-Fortification	Partial Fortification	Full Fortification	Rate Ratio*	Difference in Rate**
Rate (95% confidence interval)					
<b>New Foundland and Labrador</b>	4.56 (3.78-5.53)	1.14 (0.80-2.21)	0.76 (0.48-1.31)	0.17 (0.09-0.32)	3.80 (2.89-4.71)
<b>Prince Edward Island</b>	2.08 (1.23-3.23)	1.06 (0.33-2.58)	0 (0-0.6)	0 (0-0.62)	2.08 (1.20-2.96)
<b>Nova Scotia</b>	2.72 (2.29-3.14)	1.32 (0.91-1.87)	1.26 (0.86-1.81)	0.46 (0.31-0.68)	1.46 (0.83-2.09)
<b>Quebec</b>	1.77 (1.61-1.95)	1.27 (1.19-1.45)	0.97 (0.79-1.16)	0.55 (0.47-0.65)	0.80 (0.61-0.99)
<b>Manitoba</b>	1.54 (1.25-1.84)	0.88 (0.61-1.19)	0.93 (0.64-1.24)	0.61 (0.42-0.88)	0.62 (0.20-1.02)
<b>Alberta</b>	1.12 (0.91-1.31)	0.73 (0.63-0.91)	0.67 (0.59-0.86)	0.60 (0.46-0.79)	0.45 (0.23-0.67)
<b>British Columbia</b>	0.96 (0.78-1.15)	1.08 (0.88-1.26)	0.75 (0.66-0.93)	0.78 (0.60-1.00)	0.21 (0.01-0.42)

\* The ratio is the comparison of the full-fortification rate to the pre-fortification rate

\*\* The difference is the pre-fortification rate minus the full-fortification rate

- From 1993 to 1997 there is a stable rate, followed by a decrease from 1998 to 2000 and stabilization thereafter.
- The overall prevalence of NTDs at birth decreased from 1.58 per 1,000 births before fortification to 0.86 per 1,000 births during the full-fortification period, a 46% reduction (95% CI:40-51). The magnitude of this decrease was higher for spina bifida (53%) than for either anencephaly (38%,  $P=0.02$ ) or encephalocele (31%,  $P=0.03$ ).
- The reductions in the prevalence of NTDs in each province after folic acid fortification began show a clear east-to-west gradient both in the pre-fortification rates of defects and in the magnitude of rate reduction after fortification was fully implemented. After full implementation, geographical differences in rates almost disappeared.
- There was a proportional relationship between the baseline rate in each province and the absolute reduction in the rate after fortification was implemented. The best fit was provided by a linear function, indicating a risk reduction proportional to pre-fortification rates and starting at pre-fortification rate value of 0.6 per 1,000 births, below which the model assumed that no further reduction was possible.

**Author Conclusion:**

Food fortification with folic acid was associated with a significant reduction in the rate of NTDs in Canada. The decrease was greatest in areas in which the baseline rate was high.

**Reviewer Comments:****Research Design and Implementation Criteria Checklist: Primary Research**

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	N/A
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	N/A

  

Validity Questions		
1.	<b>Was the research question clearly stated?</b>	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	<b>Was the selection of study subjects/patients free from bias?</b>	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	No
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	<b>Were study groups comparable?</b>	???
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	???

3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	???
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	???
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
<b>4.</b>	<b>Was method of handling withdrawals described?</b>	<b>Yes</b>
4.1.	Were follow-up methods described and the same for all groups?	N/A
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	N/A
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
<b>5.</b>	<b>Was blinding used to prevent introduction of bias?</b>	<b>Yes</b>
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	Yes
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
<b>6.</b>	<b>Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?</b>	<b>Yes</b>
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	???

6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	N/A
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	N/A
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
<b>7.</b>	<b>Were outcomes clearly defined and the measurements valid and reliable?</b>	<b>Yes</b>
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	N/A
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	N/A
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	No
7.7.	Were the measurements conducted consistently across groups?	Yes
<b>8.</b>	<b>Was the statistical analysis appropriate for the study design and type of outcome indicators?</b>	<b>Yes</b>
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	No
8.6.	Was clinical significance as well as statistical significance reported?	N/A
8.7.	If negative findings, was a power calculation reported to address type 2 error?	No
<b>9.</b>	<b>Are conclusions supported by results with biases and limitations taken into consideration?</b>	<b>Yes</b>
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes

<b>10.</b>	<b>Is bias due to study's funding or sponsorship unlikely?</b>	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes